

Mayapple's Cancer-Fighting Precursor

CAMILO CANEL (K8938-1)



Mayapple is usually easy to find in the forest in the spring because of its distinctly shaped leaf.

The humble mayapple, so plentiful in the shade of forests in the southern and central United States, may soon take a more prominent place in the sun thanks to research. Scientists have found the mayapple is an excellent source of podophyllotoxin, a compound used for making cancer-fighting chemicals.

Traditionally, podophyllotoxin has been obtained from the roots of a wild Asian plant, *Podophyllum emodi*, a cousin of the mayapple. The Asian plant is found only in alpine and sub-alpine areas of the Himalaya mountains.

"*P. emodi* is prized for its podophyllotoxin, which is used as the starting material for producing the antitumor agent etoposide," says Agricultural Research Service plant physiologist Camilo Canel. He and co-inventor Frank E. Dayan are in the Natural Products Utilization Research Unit at Oxford, Mississippi.

Etoposide is the active ingredient in a drug used for the treatment of lung and testicular cancer. In chemotherapy, the drug has been shown to inhibit the activity of an enzyme essential for the replication of cancer cells, thereby preventing their spread.

CAMILO CANEL (K8938-3)



The forest floor in the southern and central United States often contains patches of mayapple.

"The problem is that *P. emodi* has been declared an endangered species because of overcollection in India," says Canel. Shrinking supplies from its native population in India—the primary collection site—have resulted in export restrictions.

The synthesis of etoposide from simple building blocks requires a costly multistep process, so many

attempts have been made to develop alternative natural sources of podophyllotoxin.

Working with scientists at the University of Mississippi-Oxford, Canel and Dayan discovered and developed a new method of extracting podophyllotoxin. With the new procedure the scientists have shown that leaves of an American weed, *P. peltatum*, commonly known as mayapple, can yield more podophyllotoxin than any other source.

"This native North American plant provides a readily available, plentiful, and renewable source of the drug," says Canel. "Given the acute toxicity of podophyllotoxin, we think that both the mayapple and the Indian species produce the compound as a form of protection from insects and other herbivores."

The ARS-Mississippi team has found an efficient way to extract podophyllotoxins, which the mayapple stores in the form of glucosides. Canel says the mayapple adds a glucose molecule to podophyllotoxins so the compound can be safely stored until the plant is attacked.

The key to extraction is to make the plant think it's under attack. By simulating an herbivore attack, Canel managed to turn on the plant's glucose-removing machinery. "This allowed the release of large amounts of stored podophyllotoxins," says Canel.

"The new extraction method is fast, efficient, and inexpensive," he says. "And mayapple leaves provide a dependable long-term supply of podophyllotoxins." If the method is adopted, increased demand for the American mayapple may make it a new alternative crop, Canel says.

The team has filed a joint patent on the new technology. Talks are in progress with pharmaceutical firms to license the technology to make this drug more widely available.—By **Hank Becker**, ARS.

This research is part of New Uses, Quality, and Marketability of Plant and Animal Products, an ARS National Program (#306) described on the World Wide Web at <http://www.nps.ars.usda.gov/programs/cppvs.htm>.

Camilo Canel is in the USDA-ARS Natural Products Utilization Research Unit, Room 2021, University of Mississippi, Oxford, MS 38677-8048; phone (662) 915-7965, fax (662) 915-1035, e-mail ccanel@olemiss.edu. ♦

CAMILO CANEL (K8938-2)



When the mayapple is under attack, it turns on defenses that activate potent toxins such as podophyllotoxins.